

B. REMARKS

Claims 1, 6, 9, 10 and 17 stand rejected under 35 U.S.C. 102(b) as being anticipated by Hale. This rejection is respectfully traversed.

The present invention, as defined broadly in Claim 1, is directed to a pharmaceutical comprising a therapeutic antibody that binds to a therapeutic target. The antibody has been modified with a peptide that reduces binding of the antibody to the therapeutic target. The modified antibody is effective for reducing an immune response against the antibody, and produces a therapeutic effect by binding to the therapeutic target. The antibody includes an antibody combining site that binds to the therapeutic target. The peptide is bound to the antibody combining site of the antibody. The pharmaceutical also includes a pharmaceutical carrier.

Hale discloses the testing of the binding of Campath antibodies to various CD52 mimotopes. In the experiments of Hale, however, the Campath antibodies were not modified.

More particularly, Hale discloses various assays, such as ELISA assays and inhibition assays, to determine the binding of unmodified Campath antibodies to various mimotopes of the CD52 epitope to which Campath binds. Such assays were conducted in order to characterize more precisely the epitope which is recognized by Campath antibodies, and to construct analogues of the epitope that would be useful in assays and for purifying unmodified Campath antibodies, as well as for further study of the antibody-antigen binding site.

Figure 8 of Hale shows that two of the mimotopes tested by Hale inhibited binding of the unmodified Campath antibody to human lymphocytes. Hale, however,

does not disclose or even remotely suggest to one of ordinary skill in the art that the Campath antibody may be modified with such mimotopes in order to provide a modified antibody.

Hale is directed solely to studying the binding of unmodified Campath antibodies to CD52 mimotopes in order to aid in developing assays and in purifying Campath antibodies, as well as studying the antibody-antigen interaction between Campath antibodies and the CD52 epitope recognized by Campath, or mimotopes thereof.

In contrast to Hale, Applicants modify an antibody with a peptide in order to inhibit binding of the antibody to a therapeutic target, and to reduce the immune response against the antibody. Although binding of the antibody to a therapeutic target is inhibited, there is some binding of the antibody to the therapeutic target, and a therapeutic effect is produced. Thus, the modified antibody provides a therapeutic effect while an immune response to the antibody is reduced. Hale does not disclose, nor does Hale even remotely suggest to one of ordinary skill in the art such a modified antibody, as claimed by Applicants. Therefore, Hale does not anticipate Applicants' claimed antibody nor does Hale render Applicants' claimed antibody obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reconsidered and withdrawn.

The claims stand rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement. This rejection is respectfully traversed.

The Examiner has taken the position that the written description of the application only reasonably conveys a therapeutic humanized anti-CD52 antibody, Campath-1H, modified by linking two different CD52 mimotopes, in which the antibody-

mimotope conjugate reduced the immune response (i.e., cytokine release) and had a therapeutic effect by binding CD52.

Contrary to the Examiner's allegations, the specification describes what the invention is as well as what the invention does. The present invention is directed to a pharmaceutical that comprises a therapeutic antibody that includes an antibody combining site, and is modified with a peptide that is bound to the antibody combining site. Those skilled in the art understand readily that different antibodies will have different antibody combining sites, and that the location of the antibody combining site of an antibody can be determined by routine experimentation. Once the antibody combining site has been determined, one can modify the antibody by binding a peptide to the antibody - combining site of the antibody by means known to those skilled in the art. In other words, once one skilled in the art has read what the modified antibody includes, one skilled in the art would be able to make the modified antibody by standard techniques known to those skilled in the art. Once the modified antibody is constructed, one skilled in the art would be able to determine through routine experimentation whether the peptide reduced binding of the antibody to the therapeutic target and reduced the immune response against the antibody. Therefore, for the above reasons and others, the specification provides a written description of the invention, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

The claims stand rejected under 35 U.S.C. 112, first paragraph, for failing to provide an enabling disclosure. This rejection is respectfully traversed.

As noted hereinabove, the Examiner has admitted that the specification is enabling for a pharmaceutical composition comprising Campath-1H modified by linkage to a CD52 mimotope selected from QTSSPSAD and QTSAAAVD.

The Examiner has misunderstood Applicants' previous arguments in that the Examiner believes that such arguments were directed to showing that one skilled in the art would be able to make and test the invention, as opposed to make and use. What Applicants assert is that one skilled in the art would know how to modify antibodies other than Campath-1H in accordance with the present invention. One skilled in the art would be able to determine, by routine experimentation how to bind peptides to antibody combining sites of other antibodies to provide modified antibodies. Once one has made a modified antibody, then one can test the modified antibody in order to determine whether binding to the therapeutic target has been reduced. Once one has tested and determined that binding of the modified antibody to the therapeutic target has been reduced, one skilled in the art then would know that such modified antibody can be used to provide a therapeutic effect while providing a reduced antibody response against the modified antibody. Thus, Applicants have enabled one skilled in the art to make, test, and use the invention, and therefore the claims are patentable under 35 U.S.C. 112, first paragraph.

The Examiner also states that even minor changes in an epitope sequence may affect the antigen binding-function of the antibody.

Applicants assert that such statement has no relevance with respect to enablement. The mere fact that the amino acid sequence of an epitope has been altered does not mean that an antibody cannot bind to an unmodified epitope. The

Examiner appears to be stating that just because an antibody may not be able to bind to a modified epitope, the antibody is not enabled. The possibility that an antibody may be able to bind to a native epitope but not to a modified epitope does not change the fact that the antibody binds to the native epitope, and therefore one skilled in the art is enabled to use the antibody.

The Examiner then states that even one amino acid difference in the peptide used for the modification of the therapeutic antibody could change dramatically the affinity or binding to the antibody combining site.

As noted hereinabove, one skilled in the art can determine whether a modified antibody has reduced binding to the therapeutic target, and whether there is a reduced antibody response against the modified antibody. If the modified antibody does not have reduced binding to the therapeutic target, and there is not a reduced antibody response against the modified antibody, then such modified antibody is not within the scope of the present invention. The mere fact that not every modified antibody is within the scope of the claimed invention does not mean that the present invention is not enabled.

In sum, the modified antibodies of the present invention may be constructed and tested by means which are known to those skilled in the art. Thus, the specification enables one skilled in the art to make modified antibodies which have reduced binding to the therapeutic target, and have a reduced immune response against the modified antibody. In the rejection, the Examiner has confused the fact that not all modified antibodies are within the scope of the present invention with the legal standard for enablement. The present invention encompasses only modified antibodies with certain

properties. Such properties can be determined readily by those skilled in the art, and the modified antibodies may be produced by techniques known to those skilled in the art. Therefore, contrary to the Examiner's allegations, the claimed invention is enabled. It is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Raymond J. Lillie". The signature is fluid and cursive, with the first name "Raymond" being more prominent and the last name "Lillie" following it.

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